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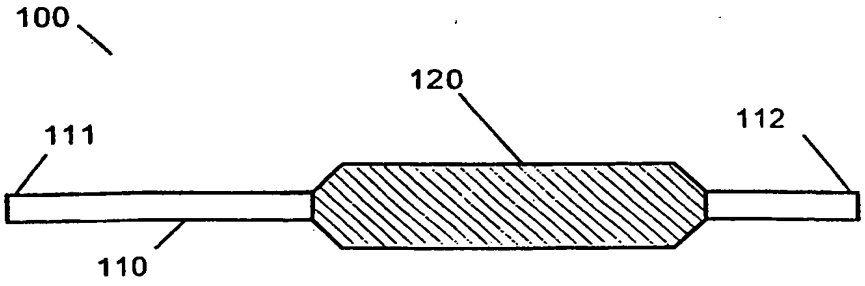

(57) Abstract

Medical devices including a substrate that are expandable from a compressed state to an expanded state; a coating on the substrate, the coating having a drug agent incorporated therein; and a sheath over the coating. The sheath is expandable from a compressed state to an expanded state and has at least one perforation therein. The medical devices are configured such that when the substrate is in a compressed state, the sheath is also in a compressed state and the perforation is substantially closed. When the substrate is in an expanded state, the sheath is also in an expanded state and the perforation is substantially open. The invention also includes a method of using the medical devices for the controlled, localized delivery of a drug agent to a target location within a mammalian body.

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LOCALIZED DELIVERY OF DRUG AGENTS

Field of the Invention

The present invention relates to methods and devices for the controlled, localized delivery of drug agents within a mammalian body.

Background of the Invention

The systemic administration of drug agents, such as by transoral or intravenous means, treats the body as a whole even though the disease to be treated may be localized. In such a case, systemic administration may not be desirable because the drug agents may have unwanted effects on parts of the body which are not to be treated, or because treatment of the diseased part of the body requires a high concentration of drug agent that may not be achievable by systemic administration.

It is therefore often desirable to administer drug agents at localized sites within the body. Common examples include cases of localized disease (*e.g.*, heart disease) or occluded body lumens. Various methods have

been proposed for such localized drug administration. For example, U.S. Patent No. 5,304,121, which is incorporated herein by reference, discloses a method of delivering water-soluble drugs to tissue at desired locations of a body lumen wall. The method generally includes the steps of impregnating a hydrogel polymer on a balloon catheter with an aqueous drug solution, inserting the catheter into a blood vessel to a desired location, and expanding the catheter balloon against the surrounding tissue to allow the release of the drug.

One of the potential drawbacks to conventional drug delivery techniques using drug-impregnated polymer coatings on balloon catheters is the possible premature diffusion of the drug out of the coating during delivery into the body. Two solutions to this problem have been proposed: the use of a removable sheath over the polymer coating, and the use of a dissolvable or meltable temporary coating over the polymer coating to protect and retain the drug agent in the coating prior to a time of desired administration at a target location. The sheath approach, however, adds considerable profile to the balloon catheter device, making access to small body lumens difficult or impracticable. Furthermore, the use of a temporary protective coating over a drug-impregnated polymer coating may place undesirable time constraints on the drug delivery procedure. Moreover, it is difficult to identify or develop temporary coatings that permit the release of the drug in a consistent and predictable manner.

In view of the potential drawbacks to conventional drug delivery techniques, there exists a need for a device and method for the controlled,

localized delivery of drug agents to target locations within a mammalian body while avoiding the premature release of drug agent during delivery.

Summary of the Invention

In one aspect, the present invention includes a medical device comprising a substrate that is expandable from a compressed state to an expanded state; a coating on the substrate and having a drug agent incorporated therein; and a sheath over the coating, the sheath being expandable from a compressed state to an expanded state and having at least one perforation therein. The medical device is configured such that when the substrate is in a compressed state, the sheath is likewise in a compressed state and the at least one perforation is substantially closed such that the drug agent does not pass through the at least one perforation. Moreover, when the substrate is in an expanded state, the sheath is likewise in an expanded state and the at least one perforation substantially opens such that the drug agent passes through the perforation.

In another aspect, the present invention includes a method for the localized delivery of drug agent to a target location within a mammalian body. The method comprises the steps of providing the medical device of the present invention; incorporating the drug agent into the coating of the device; delivering the medical device to the target location while the sheath is in a compressed state and the at least one perforation is substantially closed; and expanding the substrate to thereby expand the sheath such that the at least one perforation is substantially open. When the at least one perforation is

substantially open, the drug agent moves from the coating through the perforation and into the body.

Brief Description of the Drawings

Fig. 1 shows an expandable catheter in accordance with an embodiment of the present invention.

Figs. 2A and 2B show side and end views of an expandable sheath in accordance with an embodiment of the present invention.

Fig. 3 shows an expandable catheter and overlying expandable sheath in a compressed state, in accordance with an embodiment of the present invention.

Fig. 4 shows an expandable catheter and overlying expandable sheath in an expanded state, in accordance with an embodiment of the present invention.

Figs. 5A and 5B show side and end views of a stent used in an embodiment of the present invention.

Detailed Description

The present invention provides medical devices and methods for the controlled, localized delivery of drug agents to target locations within a mammalian body while avoiding the premature release of drug agent during delivery. The medical devices of the present invention have a simple construction, provide a minimal cross-sectional profile, and allow for the easy and reproducible loading of drug agents.

The medical device of the present invention includes any one of a number of medical devices that are applicable to the localized delivery of drug agents to within the body. When an expandable catheter is chosen as the medical device of the present invention, the expandable portion is preferably a balloon as described with specific reference to Figs. 1-4. In this embodiment, the medical device 100 comprises an expandable catheter 110 having proximal and distal ends 111, 112. Mounted towards the distal end 112 of the catheter 110 is an expandable portion 120. The expandable portion 120 is a balloon, and more preferably, a perfusion balloon, as known in the art. Such balloon catheters are conventionally used for medical procedures such as, for example, angioplasty or the placement of stents to within body lumens such as coronary arteries.

The expandable portion 120 of catheter 110 is coated with a polymer for holding the drug agent during delivery into the body. The polymer coating 130 is preferably capable of absorbing a substantial amount of drug solution. The polymer coating 130 is placed onto the expandable portion 120 by any suitable mean such as, for example, immersing the expandable portion 120 into the polymer or a solution thereof, or spraying the polymer or solution thereof onto the expandable portion 120. The polymer is typically applied to a thickness of about 1 to 10 microns, preferably about 2 to 5 microns. Very thin polymer coatings, *e.g.*, of about 0.2-0.3 microns and much thicker coatings, *e.g.*, more than 10 microns, are also possible. It is also within the scope of the present invention to apply multiple layers of polymer coating onto the

expandable portion 120 of catheter 110. Such multiple layers can be of the same or different polymer materials.

The polymer coating 130 comprises any polymeric material capable of absorbing or otherwise holding the drug agent to be delivered. The polymeric material is, for example, hydrophilic or hydrophobic, and is preferably selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters, polyacrylamides, polyethers, and copolymers thereof. Coatings from polymer dispersions such as polyurethane dispersions (BAYHDROL, etc.) and acrylic latex dispersions are also within the scope of the present invention. The preferred polymer is polyacrylic acid, as described in U.S. Pat. No. 5,091,205, the disclosure of which is incorporated herein by reference. U.S. Patent No. 5,091,205 describes medical devices coated with one or more polyisocyanates such that the devices become instantly lubricious when exposed to body fluids.

The medical device 100 includes an expandable sheath 210 (Figs. 2A & 2B), which is sized to fit over the polymer-coated expandable portion 120 of the catheter 110. The sheath 210 comprises an elastic and resilient material such that it substantially conforms to the shape of the expandable portion 120 and expands and contracts with the expandable portion 120. In a preferred embodiment, the sheath 210 is biased towards a compressed state to hold the expandable portion 120 in a compressed state when it is not expanded, thus minimizing the profile of the medical device 100.

for the construction of the sheath 210 include metallic materials such as nitinol and stainless steel, and polymeric materials such as ethylene vinyl acetate, latexes, urethanes, polysiloxanes, styrene-ethylene/butylene-styrene block copolymers, silicone rubber, SILASTIC™, aliphatic polyesters, and mixtures and copolymers thereof.

In the embodiment shown in Fig.s 2A and 2B, the sheath is a cylindrical tube having at least one perforation 220 therein. The sheath 210 is placed over the polymer-coated expandable portion 120 of the catheter 110 while in a deflated state as shown in Fig. 3. The proximal and distal ends 211, 212 of the sheath 210 are preferably attached to the catheter 110 such that the expandable portion 120 is completely covered by the sheath 210. The sheath 210 is attached to the catheter 110 by any suitable means, such as by adhesive materials and/or by winding a filament 310 (*e.g.*, suture, etc.) around its proximal and distal ends 211, 212. The sheath 210 is of minimal thickness so to minimize the profile of the medical device 100. The preferred thickness of the sheath 210 is approximately 5 mils or less.

As shown in Fig. 3, the perforation(s) in the sheath 210 is (are) preferably longitudinal slits. While it is within the scope of the invention for the sheath 210 to have a single perforation, it is preferred that the sheath 210 contain multiple perforations in the shape of longitudinal slits arranged in a staggered pattern. In one embodiment, the sheath 210 contains multiple longitudinally-oriented perforations which measure approximately 0.75 cm in length, and are spaced approximately 0.25 cm apart in a longitudinal direction and approximately 15° apart in a radial direction.

The medical device 100 is delivered into the body while the expandable portion 120 is in a deflated shape as shown in Fig. 3. As such, the sheath 210 is in a compressed state and the perforations 220 are substantially closed such that the drug agent in the polymer coating 130 does not pass through the perforations 220. Delivery of the medical device 100 into the body and to a target location occurs, for example, through a body lumen (*e.g.*, coronary arteries, portal vein, ileofemoral vein, etc.) by torquing or other known techniques.

Once the medical device 100 is positioned to a target location within the body, the expandable portion 120 is expanded as shown in Fig. 4 to facilitate the release of drug agent from the polymer coating 130. The expandable sleeve 210 is constructed so that it will not rupture when the underlying expandable portion 120 of the catheter 110 is fully expanded. When the expandable portion 120 is in an expanded state, the sheath 210 is also in an expanded state and the perforations 220 become substantially open such that the drug agent in the polymer coating 130 passes through the perforations 220. The drug agent is released from the polymer coating 130 by any suitable mechanism, such as by diffusion or pressure-enhanced release.

The drug agents used in the present invention include, for example, pharmaceutically active compounds, proteins, oligonucleotides, genes, DNA compacting agents, gene/vector systems (*i.e.*, anything that allows for the uptake and expression of nucleic acids), nucleic acids (including, for example, DNA, cDNA, RNA, antisense DNA or RNA), and viral, liposomes and cationic polymers that are selected from a number of types depending on the

desired application. For example, biologically active solutes include anti-thrombogenic agents such as heparin, heparin derivatives, urokinase, and PPack (dextrophenylalanine proline arginine chloromethylketone); anti-proliferative agents such as enoxaprin, angiopeptin, or monoclonal antibodies capable of blocking smooth muscle cell proliferation, hirudin, and acetylsalicylic acid; anti-inflammatory agents such as dexamethasone, prednisolone, corticosterone, budesonide, estrogen, sulfasalazine, and mesalamine; antineoplastic/antiproliferative/anti-miotic agents such as paclitaxel, 5-fluorouracil, cisplatin, vinblastine, vincristine, epothilones, endostatin, angiostatin and thymidine kinase inhibitors; anesthetic agents such as lidocaine, bupivacaine, and ropivacaine; anti-coagulants such as D-Phe-Pro-Arg chloromethyl keton, an RGD peptide-containing compound, heparin, antithrombin compounds, platelet receptor antagonists, anti-thrombin anticodies, anti-platelet receptor antibodies, aspirin, protaglandin inhibitors, platelet inhibitors and tick antiplatelet peptides; vascular cell growth promotors such as growth factor inhibitors, growth factor receptor antagonists, transcriptional activators, and translational promotors; vascular cell growth inhibitors such as growth factor inhibitors, growth factor receptor antagonists, transcriptional repressors, translational repressors, replication inhibitors, inhibitory antibodies, antibodies directed against growth factors, bifunctional molecules consisting of a growth factor and a cytotoxin, bifunctional molecules consisting of an antibody and a cytotoxin; cholesterol-lowering agents; vasodilating agents; and agents which interfere with endogeneus vascoactive mechanisms. These and other compounds are added to the polymer coating

using similar methods and routinely tested as set forth in the specification. Any modifications are routinely made by one skilled in the art.

Polynucleotide sequences useful in practice of the invention include DNA or RNA sequences having a therapeutic effect after being taken up by a cell. Examples of therapeutic polynucleotides include anti-sense DNA and RNA; DNA coding for an anti-sense RNA; or DNA coding for tRNA or rRNA to replace defective or deficient endogenous molecules. The polynucleotides of the invention can also code for therapeutic polypeptides. A polypeptide is understood to be any translation product of a polynucleotide regardless of size, and whether glycosylated or not. Therapeutic polypeptides include as a primary example, those polypeptides that can compensate for defective or deficient species in an animal, or those that act through toxic effects to limit or remove harmful cells from the body. In addition, the polypeptides or proteins that can be incorporated into the polymer coating 130, or whose DNA can be incorporated, include without limitation, angiogenic factors including acidic and basic fibroblast growth factors, vascular endothelial growth factor, epidermal growth factor, transforming growth factor α and β, platelet-derived enotheial growth factor, platelet-derived growth factor, tumor necrosis factor α, hepatocyte growth factor and insulin like growth factor; growth factors; cell cycle inhibitors including CD inhibitors; thymidine kinase ("TK") and other agents useful for interfering with cell proliferation, including agents for treating malignancies. Still other useful factors, which can be provided as polypeptides or as DNA encoding these polypeptides, include the family of bone morphogenic proteins ("BMP's"). The known proteins include BMP-2, BMP-3,

BMP-4, BMP-5, BMP-6 (Vgr-1), BMP-7 (OP-1), BMP-8, BMP-9, BMP-10, BMP-11, BMP-12, BMP-13, BMP-14, BMP-15, and BMP-16. Currently preferred BMP's are any of BMP-2, BMP-3, BMP-4, BMP-5, BMP-6 and BMP-7. These dimeric proteins can be provided as homodimers, heterodimers, or combinations thereof, alone or together with other molecules. Alternatively or, in addition, molecules capable of inducing an upstream or downstream effect of a BMP can be provided. Such molecules include any of the "hedgehog" proteins, or the DNA's encoding them.

The drug agent is introduced into the polymer coating 130 by any suitable method. For example, the drug agent is placed in solution, which is thereafter applied to the polymer coating 130 by any suitable means, including dipping the polymer coating 130 into the drug solution or by applying the solution onto the coating 130 such as by pipet or spraying. In the former method, the amount of drug loading is controlled by regulating the time the polymer is immersed in the drug solution, the extent of polymer cross-linking, the concentration of the drug in the solution and/or the amount of polymer coating. In another embodiment of the invention, the drug is incorporated directly into the polymer prior to the application of the polymer as a coating onto a medical device. The drug agent can be applied to the polymer coating 130 either before or after the sheath 210 is placed over the coating 130. For example, if applied after the sheath 210 is placed over the coating 130, the expandable portion 120 is expanded to thereby open the perforations 220 in the sheath 210 as shown in Fig. 4. The drug agent is thereafter incorporated into the polymer coating 130 through the open perforations 220 by any suitable

means such as, for example, dipping the medical device 100 into a solution of drug agent. The method of incorporating the drug agent into the coating 130 through the open perforations 220 is generally preferred, especially where the polymer coating 130 is loaded multiple times with the same or different drug agents.

The release profile of the drug from the polymer coating 130 is determined by many factors including the drug solubility, the thickness and porosity of the polymer coating, and the number and size of perforations 220 in the sleeve 210. When an expandable member such as a balloon catheter is used to administer the drug, pressure can be used to increase the rate of drug transfer to the tissue. An increase in pressure increases the diameter of the balloon and therefore the diameter of the surrounding tissue (if contacted by the balloon), thereby increasing the surface area for drug transfer. The amount of drug that is delivered per unit time is therefore increased. An increase in the rate of drug release from the polymer coating 130 is also accomplished by increasing both the number and size of perforations 220 in the sleeve 210.

During drug administration, a substantial amount of the drug agent contained in the polymer coating 130 is diffused into the affected area. The inflation pressure needed to expand the expandable portion 120 of catheter 110 is typically in the range of about 1 to 20 atm. When the expandable portion 120 comprises a balloon, it is formed of any suitable material such as vinyl polymers such as polyethylene; polyesters such as polyethylene terephthalate; polyamides such as nylon; polyolefins and

copolymers thereof (*e.g.*, Selar, Pebax, Surlyn, Hytrel, etc.). The balloon is optionally a perfusion balloon, which allows blood to perfuse the catheter to prevent ischemia during delivery. A perfusion balloon is particularly preferred for long arterial delivery times and when the delivery drug is only very slightly soluble in water.

In one embodiment, the medical device 100 of the present invention includes a stent 510 (Figs. 5A & 5B) for placement in a body lumen. The present invention can thus be used for the dual purpose of localized drug delivery and stent placement. As known in the art, stents are tubular support structures that are implanted inside tubular organs, blood vessels or other tubular body lumens. The stent used with the present invention is of any suitable design, and is either self-expanding or balloon-expandable. The stent is made of any suitable metallic (*e.g.*, stainless steel, nitinol, tantalum, etc.), polymeric (*e.g.*, polyethylene terephthalate, polyacetal, polylactic acid, polyethylene oxide - polybutylene terephthalate copolymer, etc.) or biodegradable material. The stent 510 is preferably metallic and configured in a mesh design, as shown in Figs. 5A and 5B. When used with the present invention, the stent 510 is placed over the sheath 210 when each of the expandable portion 120, the sheath 210, and the stent 510 are in a compressed state. The medical device 100 is thereafter delivered to a target location within the body, as previously described. In this embodiment, the target location is situated within a body lumen. When the expandable portion 120 is expanded to release the drug agent from the polymer coating 130, the stent 510 is likewise expanded. After the drug agent has been released from

the polymer coating 130, the expandable portion 120 is compressed or deflated such that the sheath 210 is compressed with the expandable portion 120. The stent 510, however, remains in its expanded state within the body lumen.

The medical device of the present invention is optionally used to accomplish electroporation, in which short pulses of high electric fields are applied to a target location in the body to thereby cause cell membranes to become porous so that drug agents can diffuse therein. Any suitable modification of the medical device is made to facilitate electroporation as is known in the art, such as, for example, the inclusion of electrodes. The medical device of the present invention may also be modified, as is known in the art, for accomplishing iontophoresis in which a current is applied at the target location to promote the delivery of ionic drug agents.

The present invention provides a system and method for the localized delivery of drug agent to target locations within a mammalian body. Although the present invention has been described with respect to several exemplary embodiments, there are many other variations of the above-described embodiments which will be apparent to those skilled in the art, even where elements have not explicitly been designated as exemplary. It is understood that these modifications are within the teaching of the present invention, which is to be limited only by the claims appended hereto.

What is claimed is:

1. A medical device, comprising:

a substrate that is expandable from a compressed state to an expanded state;

a coating on said substrate, said coating having a drug agent incorporated therein; and

a sheath over said coating, said sheath being expandable from a compressed state to an expanded state and having at least one perforation therein;

wherein when said substrate is in a compressed state, said sheath is in a compressed state and said at least one perforation is substantially closed such that said drug agent does not pass through said at least one perforation; and

wherein when said substrate is in an expanded state, said sheath is in an expanded state and said at least one perforation is substantially open such that said drug agent passes through said at least one perforation.

2. The device of claim 1, wherein said coating comprises a polymer selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters, polyacrylamides,

polyethers, polyurethane dispersions, acrylic latex dispersions, and mixtures and copolymers thereof.

3. The device of claim 1, wherein said drug agent is selected from the group consisting of pharmaceutically active compounds, proteins, oligonucleotides, DNA compacting agents, recombinant nucleic acids, gene/vector systems, and nucleic acids .

4. The device of claim 1, wherein said sheath comprises a material selected from the group consisting of ethylene vinyl acetate, latexes, urethanes, polysiloxanes, styrene-ethylene/butylene-styrene block copolymers, aliphatic polyesters, and mixtures and copolymers thereof; and nitinol and stainless steel.

5. The device of claim 1, wherein said at least one perforation is in the shape of a longitudinal slit.

6. The device of claim 5, wherein said sheath comprises a plurality of perforations arranged in a staggered pattern.

7. The device of claim 1, wherein said substrate comprises at least part of a balloon portion of a balloon catheter.

8. The device of claim 7, wherein said sheath is tubular and surrounds said balloon portion of said balloon catheter, said tubular sheath having proximal and distal ends.

9. The device of claim 8, wherein said proximal and distal ends of said sheath are attached to said balloon catheter such that said balloon portion is completely covered by said sheath.

10. The device of claim 9, wherein said proximal and distal ends of said sheath are attached to said balloon catheter by an adhesive.

11. The device of claim 9, further comprising a filament around said proximal and distal ends of said sheath.

12. A method for the localized delivery of a drug agent to a target location within a mammalian body, comprising the steps of:

providing a medical device comprising:

a substrate that is expandable from a compressed state to an expanded state;

a coating on said substrate; and

a sheath over said coating, said sheath being expandable from a compressed state to an expanded state and having at least one perforation therein;

wherein when said substrate is in a compressed state, said sheath is in a compressed state and said at least one perforation is substantially closed; and

wherein when said substrate is in an expanded state, said sheath is in an expanded state and said at least one perforation in said expandable sheath is substantially open;

incorporating said drug agent into said coating;

delivering said medical device to said target location while said sheath is in a compressed state and said at least one perforation is substantially closed; and

expanding said substrate to thereby expand said sheath to an expanded state such that said at least one perforation is substantially open, whereby the drug agent passes through said at least one perforation.

13. The method of claim 12, wherein said step of incorporating the drug agent into said coating comprises the steps of:

expanding said substrate to thereby expand said sheath such that said at least one perforation is substantially open;

exposing said drug agent to said coating through said at least one perforation while said at least one perforation is substantially open; and

compressing said substrate to thereby compress said sheath such that said at least one perforation is substantially closed.

14. The method of claim 13, wherein said drug agent is exposed to said coating by immersing at least part of said medical device into a solution comprising said drug agent.

15. The method of claim 12, wherein said coating comprises a polymer selected from the group consisting of polycarboxylic acids, cellulosic polymers, gelatin, polyvinylpyrrolidone, maleic anhydride polymers, polyamides, polyvinyl alcohols, polyethylene oxides, glycosaminoglycans, polysaccharides, polyesters, polyacrylamides, polyethers, polyurethane dispersions, acrylic latex dispersions, and mixtures and copolymers thereof.

16. The method of claim 12, wherein said drug agent is selected from the group consisting of pharmaceutically active compounds, proteins, oligonucleotides, genes, DNA compacting agents, gene/vector systems, and nucleic acids.

17. The method of claim 12, wherein said sheath comprises a material selected from the group consisting of ethylene vinyl acetate, latexes, urethanes, polysiloxanes, styrene-ethylene/butylene-styrene block copolymers, aliphatic polyesters, and mixtures and copolymers thereof; and nitinol and stainless steel.

18. The method of claim 12, wherein said at least one perforation is in the shape of a longitudinal slit.

19. The method of claim 18, wherein said at least one perforation comprises a plurality of perforations arranged in a staggered pattern.

20. The method of claim 12, wherein said substrate comprises at least part of a balloon portion of a balloon catheter.

21. The method of claim 20, wherein said sheath is tubular and surrounds said balloon portion of said balloon catheter, said tubular sheath having proximal and distal ends.

22. The method of claim 21, wherein said proximal and distal ends of said sheath are attached to said balloon catheter such that said balloon portion is completely covered by said sheath.

23. The method of claim 12, wherein said medical device comprises an electroporation catheter.

24. The method of claim 12, wherein said medical device comprises an iontophoresis catheter.

25. A medical device, comprising:

a catheter comprising a balloon portion that is expandable from a compressed state to an expanded state;

a polymer coating on said balloon portion, said coating having a drug agent incorporated therein; and

a tubular sheath over said coating, said sheath being expandable from a compressed state to an expanded state and having a plurality of perforations therein, said perforations being arranged in a staggered pattern; wherein

the proximal and distal ends of said sheath are attached to said catheter such that said balloon portion is completely covered by said sheath;

when said balloon portion is in a compressed state, said sheath is in a compressed state and said perforations are substantially closed such that said drug agent does not pass through said perforations; and

when said balloon portion is in an expanded state, said sheath is in an expanded state and said perforations are substantially open such that said drug agent passes through said perforations.

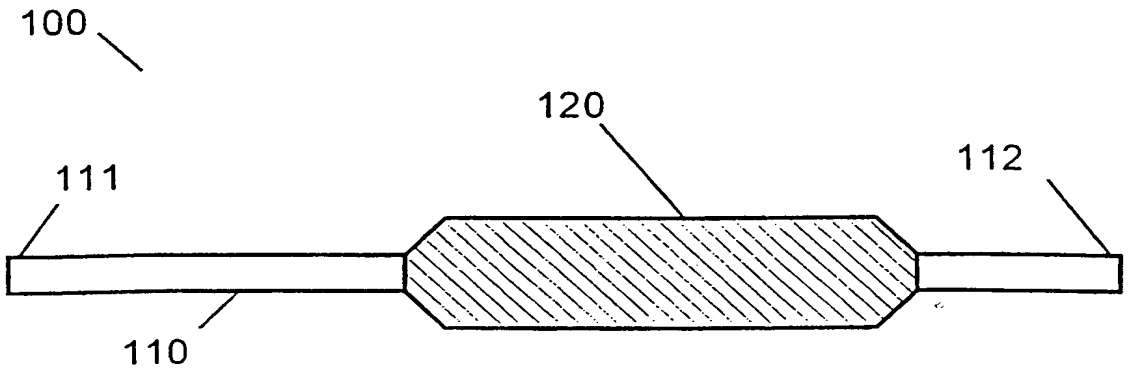

FIG. 1

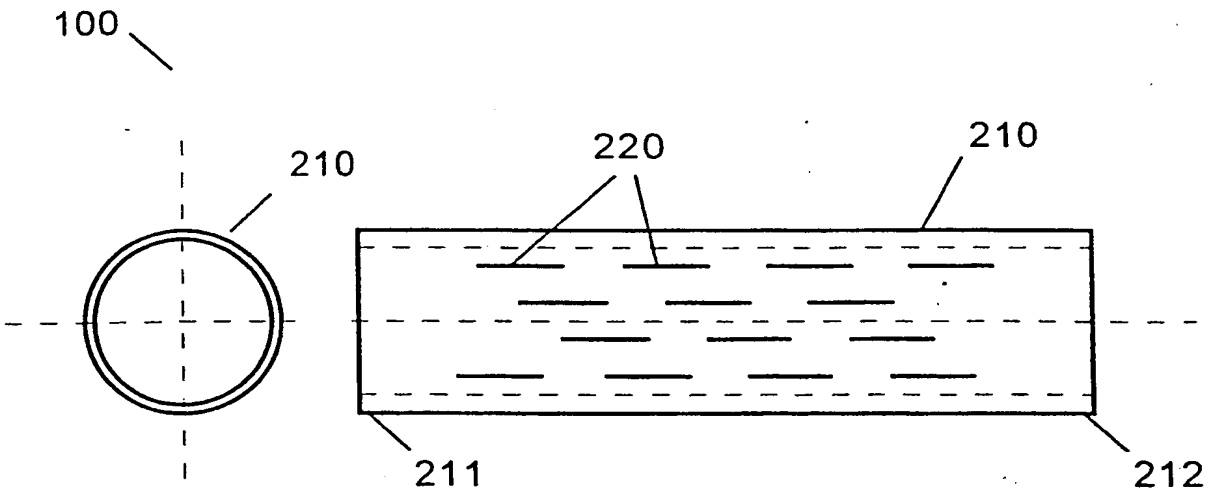

FIG. 2A FIG. 2B

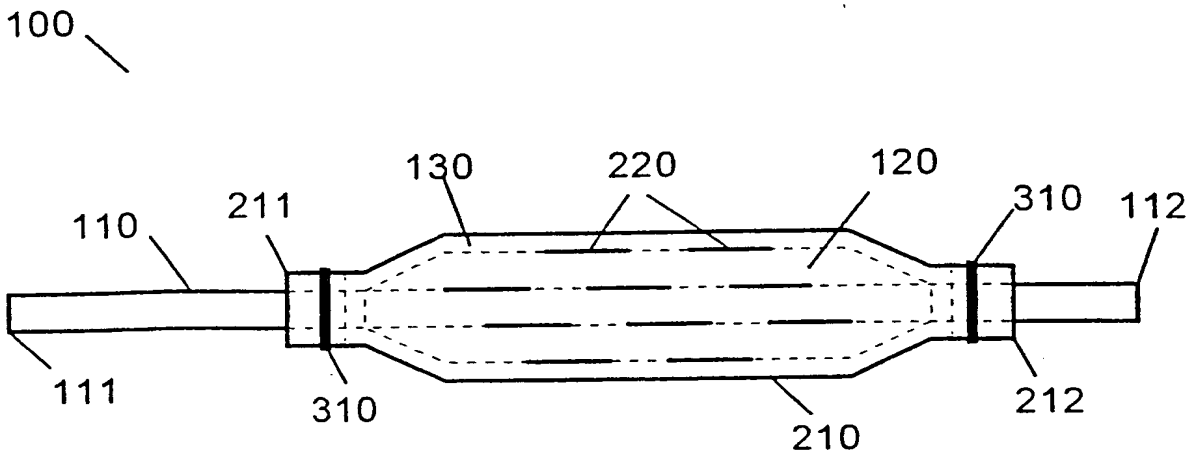

FIG. 3

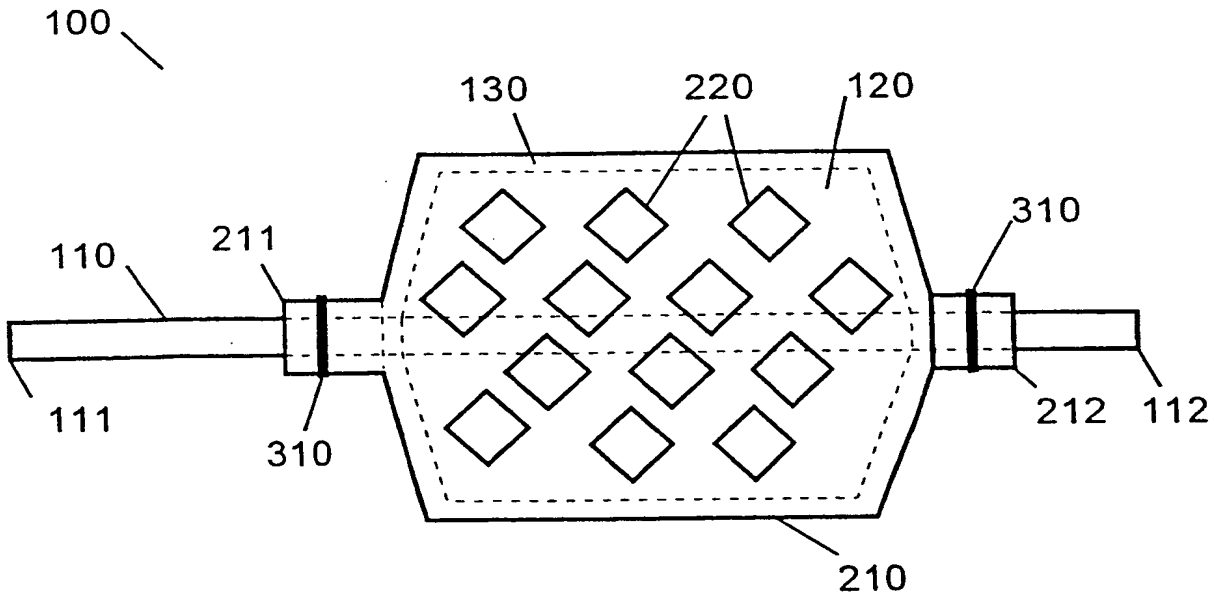

FIG. 4

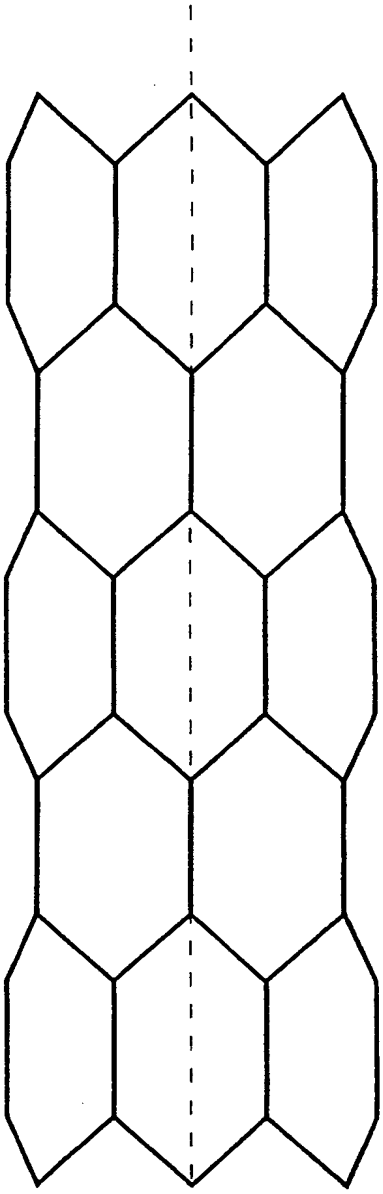

FIG. 5B

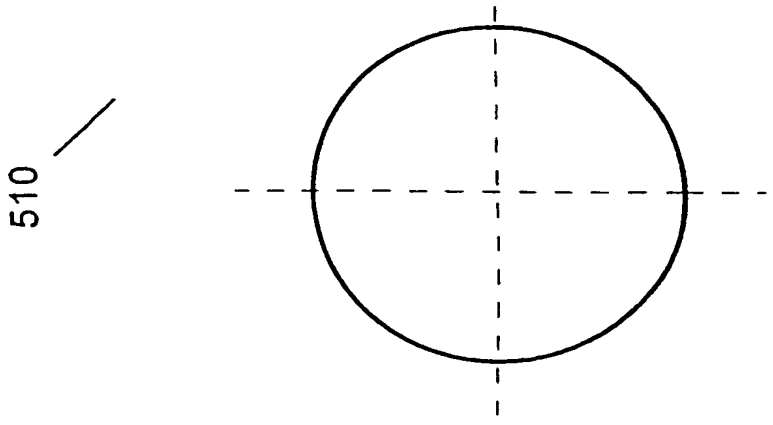

FIG. 5A

INTERNATIONAL SEARCH REPORT

International Application No
PC./US 99/10909

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61L29/00 A61L31/00 A61M29/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61L A61M A61F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 835 673 A (SCHNEIDER USA INC) 15 April 1998 (1998-04-15) abstract	1-4,7-25
A	US 5 304 121 A (SAHATJIAN RONALD) 19 April 1994 (1994-04-19) cited in the application column 1, line 44 - column 2, line 68	1-25

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
8 September 1999	17/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Muñoz, M

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

ɔrnational application No.
PCT/US 99/ 10909

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: –
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box 1.1

Although claims 12-24 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box 1.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte[illegible]tional Application No
PC[illegible]/US 99/10909

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0835673 A	15-04-1998	CA 2217945 A	10-04-1998
		JP 10118195 A	12-05-1998
US 5304121 A	19-04-1994	CA 2098984 A	29-06-1992
		DE 69131486 D	02-09-1999
		EP 0565604 A	20-10-1993
		EP 0920843 A	09-06-1999
		JP 6503984 T	12-05-1994
		WO 9211896 A	23-07-1992
		US 5674192 A	07-10-1997
		US 5843089 A	01-12-1998
		WO 9211895 A	23-07-1992

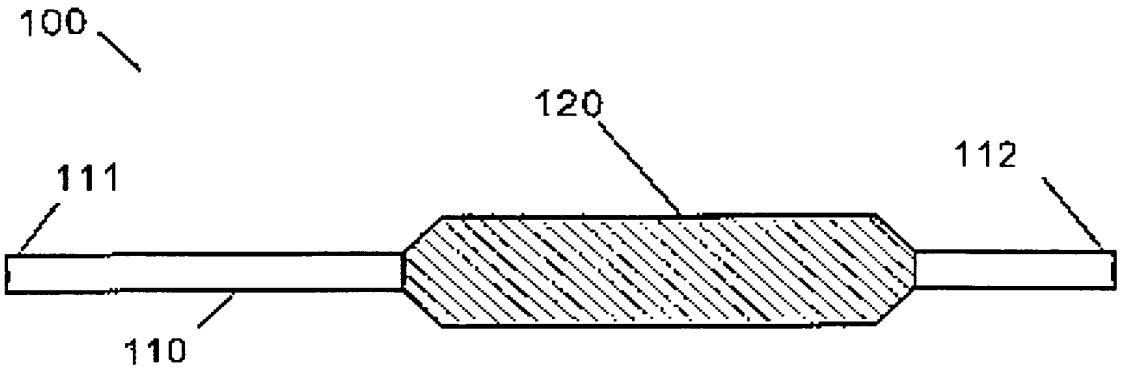

FIG. 1

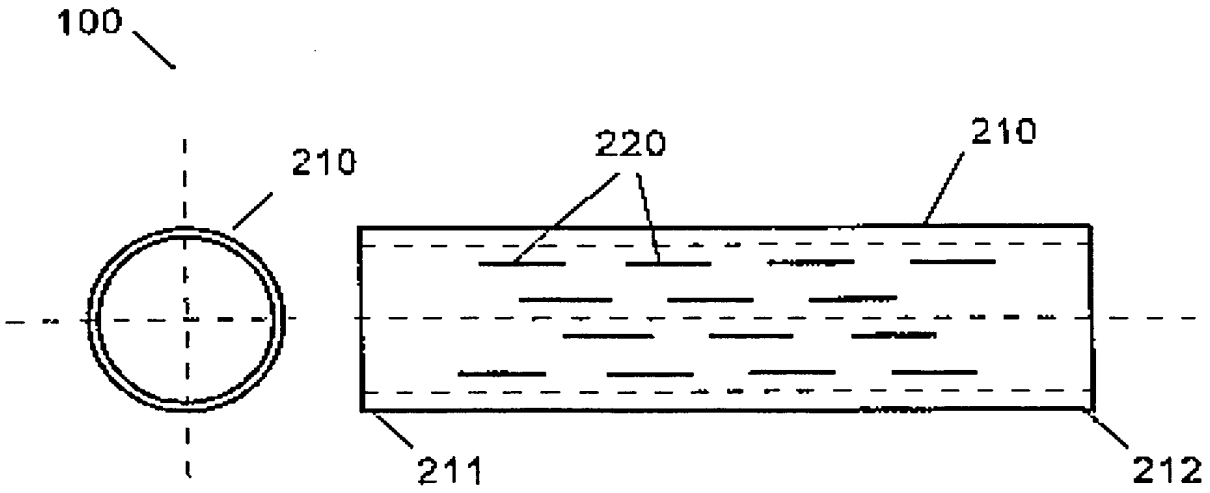

FIG. 2A FIG. 2B

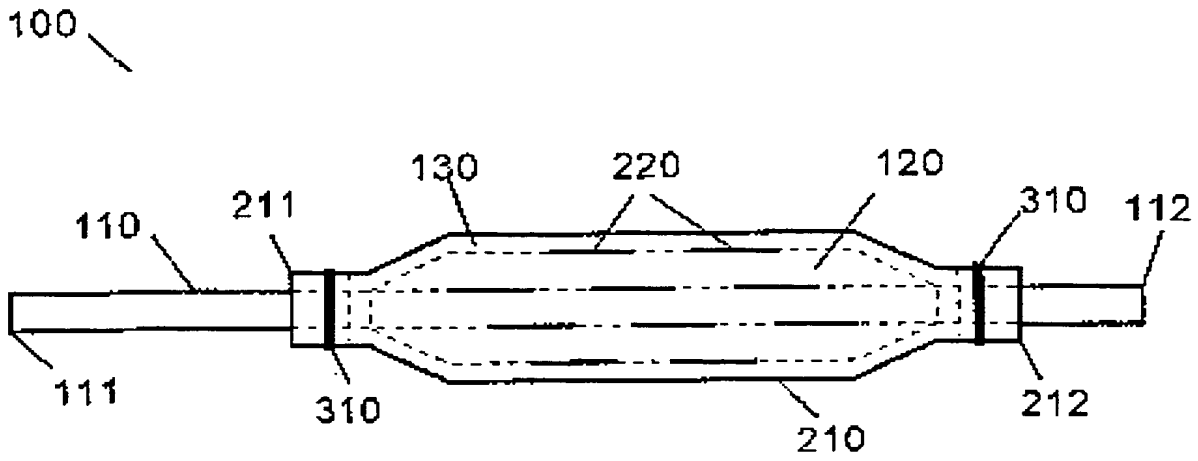

FIG. 3

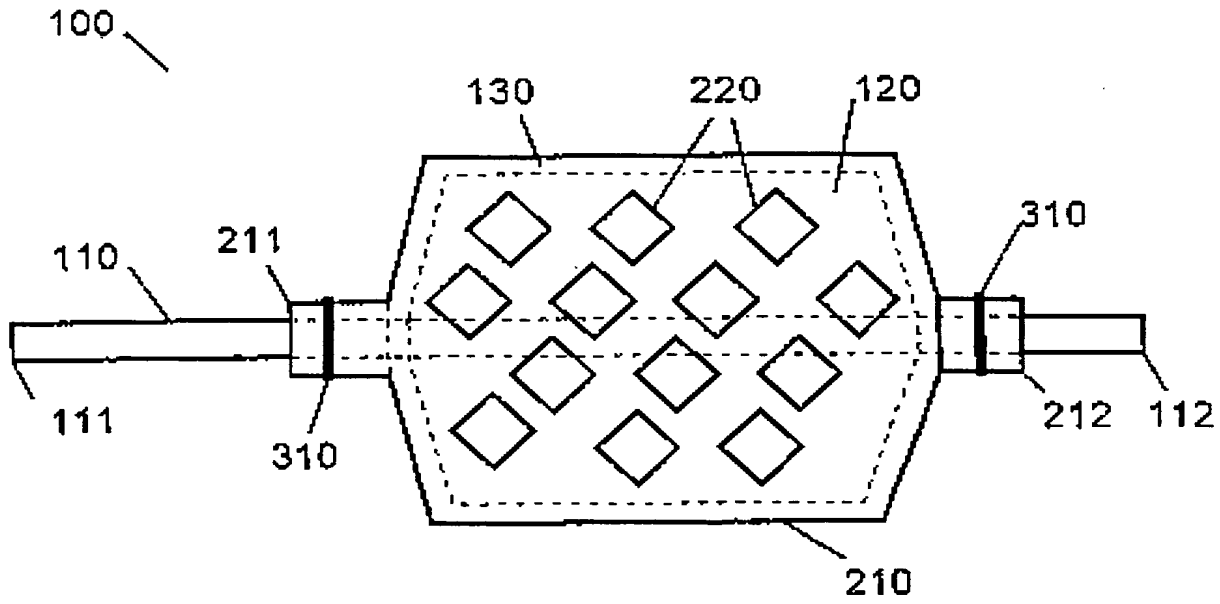

FIG. 4

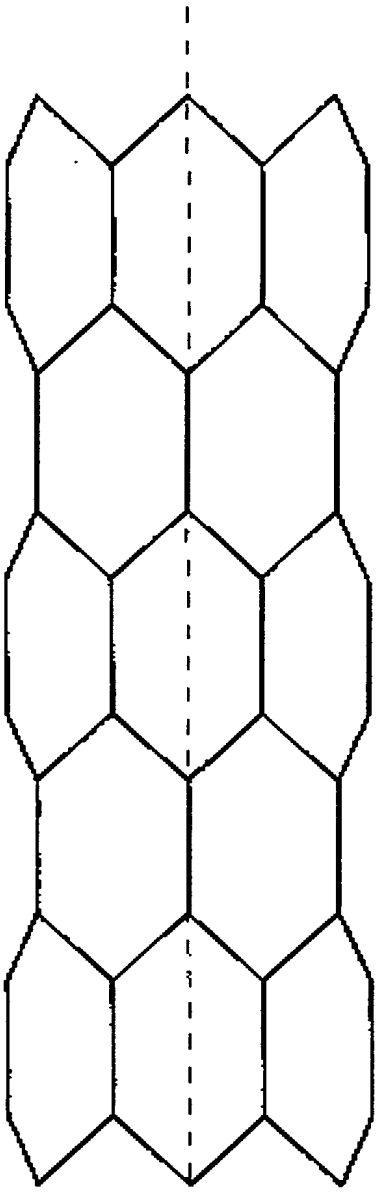

FIG. 5B

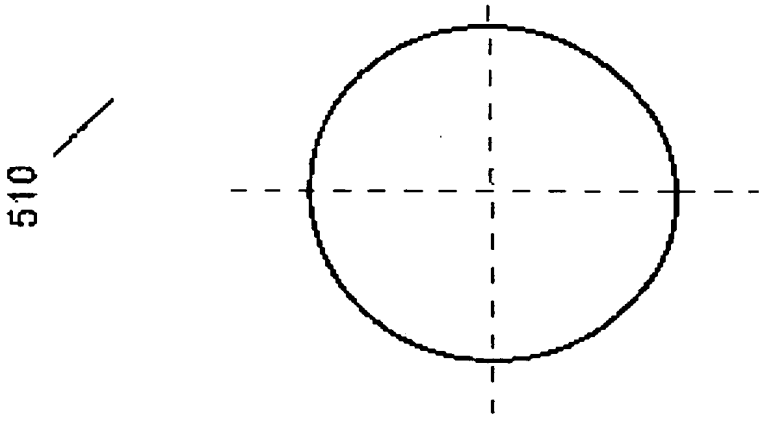

FIG. 5A